Remarks

Claims 1-4, 6-15, 18, 19, 37, 38, 40, 41, 50, 52-57 and 61-64 are pending in this application. Claims 1-4, 6-15, 18, 19 and 50 were previously withdrawn from consideration by the Examiner. Claims 37, 38, 40, 41, 50, 52-57 and 61-64 remain rejected. New claims 65-66 are added herein. Support for new claim 65 can be found throughout the specification, such as on page 7, lines 11-15. Support for new claim 66 can be found throughout the specification, such as on page 37, lines 14-15.

Applicants believe no new matter is added herein. Reconsideration of the subject application is respectfully requested. Applicants expressly reserve the right to file an Appeal.

Rejections Under 35 U.S.C. § 103 (a)

Claims 37-38, 40-41, 50, 52-57 and 61-64 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Ivins et al., (Eur. J. Epidemiol., March 1988, Vol. 4, No. 1, pages 12-19) in view of Vethelyi et al. (The Journal of Immunology, February 15, 2002, Vol. 168, pages 1659-1663) and Jones et al., (Vaccine, 1999, Vol. 17, pages 3065-3071). Applicants respectfully disagree with this rejection.

Ivins *et al.* teach the Anthrax Vaccine Adsorbed (AVA) vaccine, and that adjuvants containing alum or aluminum hydroxide are suboptimal.

Verthelyi *et al.* teach the use of CpG oliodeoxynucletides (ODN) as vaccine adjuvants. Verthelyi et al. teach that there are two types of CpG ODN, K-type oligonucleotides (see page 1659) "have phosphorothioate backbones, encode multiple TCGTT and/or TCGTA motifs (CpG motif is underlined), trigger the maturation of plasmacytoid DC, and stimulate the production of IgM and IL-6." D-type oligonucleotides "have mixed phosphodiester/phosphorothioate backbones and contain a single hexameric purine/pyrimidine/CG/purine/pyrimidine motif flanked by self-complementary bases that form a stem-loop structure capped at the 3' end by a poly G tail." Verthelyi *et al.* teach that D-type oligonucleotides were superior to K-type oligonucleotides in enhancing the immune response following vaccination in primates.

Jones *et al.* teaches the use of an oligonucleotide having the nucleotide sequence of SEQ ID NO: 200 as an adjuvant for a vaccine against malaria, a disease caused by a protozoan parasite (*Plasmodium falciparum*).

In making the rejection, the Office action alleges that the claimed invention is simple substitution of one known element for another to obtain predictable results, and that the results are

completely predictable. Applicants respectfully disagree.

Unpredictability

Based on the teachings of the prior art, it would not have been predictable that a CpG oligonucleotide comprising the nucleotide sequence of CpG 7909 (SEQ ID NO: 200) would enhance the immunogenicity of a vaccine against *Bacillus anthracis*. Although Jones *et al.* teaches the use of an oligonucleotide having the nucleotide sequence of SEQ ID NO: 200 as an adjuvant for a vaccine against malaria, a disease caused by a protozoan parasite (*Plasmodium falciparum*), one would not have been able to predict that the same oligonucleotide would enhance the immunogenicity of a vaccine against *Bacillus anthracis*, a bacterial pathogen. As previously discussed, Su *et al.* (*Infect. Immun.* 71(9):5178-5187, 2003, a copy submitted with the prior response), teach that it is not predictable that adjuvants that are effective with other types of vaccines are able to enhance an immune response against intracellular pathogens, including *Plasmodium* species. Protective immune responses against *Bacillus anthracis* require production of neutralizing antibodies.

Thus, it would not have been predictable that an adjuvant for a vaccine against an intracellular pathogen would be successful in enhancing an immune response when used in combination with a vaccine against a bacterial pathogen. Furthermore, Threadgill *et al.* (*Vaccine* 16(1):76-82, 1998, copy submitted previously), teach that administration of CpG oligonucleotide in combination with a bacterial (*Pseudomonas aeruginosa*) vaccine, actually diminishes the bacteria-specific antibody response. Given the teachings of Threadgill *et al.*, one of skill in the art would not have predicted that a CpG oligonucleotide would enhance the immunogenicity of a vaccine against a bacterial pathogen.

In yet another model, rhesus macaques were immunized with a candidate leishmania vaccine (heat-killed leishmania vaccine, HKLV) plus either "K" or "D" ODN. Animals vaccinated with HKLV alone and then challenged with *L. major* developed large cutaneous lesions. Monkeys vaccinated with HKLV plus "K" ODN also developed large lesions, although somewhat more slowly than controls. This result confirmed that not all CpG ODN improve vaccine-induced immunity. By comparison, animals immunized with HKLV plus "D" type ODN had significantly smaller lesions consistent with a reduced parasite burden. PBMC from these animals also had a higher proportion of cells that were stimulated by leishmania antigens to secrete IFN in vitro that did those immunized with HKLV alone (Klinman, Expert Review of Vaccines, 5(3): 365-369, 2006, copy submitted herewith).

In the second double-blind study, CpG ODN was co-administered with the Fluarix influenza vaccine. Inclusion of CpG ODN did not increase the Ab response of naive recipients when compared to Fluarix alone, but did increase antibody titers among subjects with pre-existing anti-flu antibodies. PBMC from CpG ODN vaccinated subjects responded to *in vitro* re-stimulation by secreting significantly higher levels of IFN than did PBMC from control vaccinees. No serious adverse events attributed to the use of CpG ODN were observed. None of the subjects exposed to CpG ODN developed signs or symptoms of autoimmune disease (Klinman, Expert Review of Vaccines, 5(3): 365-369, 2006). Thus, for any specific vaccine, it cannot be predicted (1) if CpG ODN will be an effective adjuvant, or (2) the broad class of CpG ODN (D or K) that will be efficacious, let alone (3) the particular nucleotide sequence that will be efficacious.

Optimization

The Office action states that "the use of an optimal CpG oligonucoleotide is expected to yield optimal results" (see page 5). This statement could be made for any invention. Using this reasoning, the use of an optimal combination of drugs, such as HAART, would be expected to be an optimal treatment for AIDS. Similarly, the use of an optimal chemotherapeutic regimen would be expected to provide the optimal tumor reduction. If it one were to combine every therapeutic agent with every other therapeutic agent, ultimately one could arrive at every therapeutic intervention. Thus, based on the Examiner's reasoning, no combinatorial therapeutic treatment is patentable. This is clearly incorrect, as many patents are granted relating to combinatorial therapy (see, for example: U.S. Patent No. 7,498,030; U.S. Patent No. 7,488,491; U.S. Patent No. 7,462,642). It is the identification of the specific agents that provide an unexpectedly superior result for the treatment of a specific disease that imparts patentability.

The efficacy of ODN7909 (SEQ ID NO: 200) is unpredictable

The cited references simply do not provide a basis for the selection of ODN 7909 (SEQ ID NO: 200), and it's use with an anthrax vaccine, let alone AVA.

As discussed above, the prior art, such as Su *et al.* (*Infect. Immun.* 71(9):5178-5187, 2003), teach that it is not predictable that adjuvants that are effective with other types of vaccines are able to enhance an immune response against intracellular pathogens, including *Plasmodium* species.

Threadgill *et al.* (*Vaccine* 16(1):76-82, 1998), teach that administration of CpG oligonucleotide in combination with a bacterial (*Pseudomonas aeruginosa*) vaccine, actually diminishes the bacteria-specific antibody response. Thus, there is no rationale to use CpG 7909, as taught by Jones et al., for inclusion in a completely different vaccine.

The examiner has not provided any rationale to lead one of skill in the art to select CpG 7909 (SEQ ID NO: 200) for use with an anthrax vaccine. Klinman et al. (*Expert.Rev.Vaccines.* 2:305-315, 2003) teach that there are several types of CpG ODN, and that mice and human respond differently to different CpG nucleic acid sequences. Klinman et al. teach that D ODN increase an IgG anti-ovalbumin (OVA) response by 470-fold after primary immunization, while K ODN (such as CpG 7909) only induce the IgG anti-ovalbumin (OVA) response by 35-fold after primary immunization. Thus, Klinman et al. conclude that D ODN are particularly effective for boosting antigen-specific immune response in primates.

Klinman et al. also disclose that rhesus macaques were immunized with a candidate leishmania vaccine (heat-killed leishmania vaccine, HKLV) plus either "K" or "D" ODN. Animals vaccinated with HKLV alone and then challenged with *L. major* developed large cutaneous lesions. Monkeys vaccinated with HKLV plus "K" ODN also developed large lesions, although somewhat more slowly than controls. This result confirmed that not all CpG ODN improve vaccine-induced immunity in naïve subjects. By comparison, animals immunized with HKLV plus "D" type ODN had significantly smaller lesions consistent with a reduced parasite burden. Thus, if one of skill in the art were to try to optimize immunogenicity, they would proceed with D (and not K) ODN, and certainly would not select CpG 7909 (SEQ ID NO: 200), which is a "K" type ODN.

Even if one were to proceed with a K ODN, there is no guarantee of success with any ODN sequence, let alone CpG 7909 (SEQ ID NO: 200). Klinman et al. describe two clinical trial conducted with K ODN. In one trial, a specific K type CpG ODN was used in combination in a hepatitis B vaccine. Addition of the ODN resulted in an increased immune response to the vaccine as compared to individuals immunized with the vaccine alone. However, when a specific K type CpG ODN was administered in combination with an influenza vaccine, the addition of the CpG ODN had no effect on the naïve recipients. Klinman et al. conclude that combining CpG ODN with a vaccine can be effective. However, Klinman et al. conclude that efforts are needed to identify ODN within the different classes that are optimally active in human when co-administered with different vaccines.

Thus, Klinman et al. provide evidence that the utility of any specific ODN in combination with a specific vaccine cannot be predicted.

The Unexpected Superior Result is Maintained in the Clinical Setting

The Office action alleges that the evidence presented documenting the unexpected superior result obtained with AVA and CpG 7909 is not sufficient evidence, because CpG 7909 "had on average a 17-fold higher toxin neutralizing titer than those immunized with AVA alone; however, such is not sufficient to demonstrate or evidence unexpected results for ODN has been established as the optimal CpG olignucletide for human use." Applicants respectfully disagree.

At the outset, the Applicants would like to remind the Examiner that requiring evidence from clinical trials is not an appropriate standard. With regard to an asserted therapeutic utility of a composition, MPEP § 2107.03 states:

> "As a general matter, evidence of pharmacological or other biological activity of a compound will be relevant to an asserted therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility. *Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *Nelson v. Bowler*, 626 F.2d 853, 206 USPQ 881 (CCPA 1980). An applicant can establish this reasonable correlation by relying on statistically relevant data documenting the activity of a compound or composition, arguments or reasoning, documentary evidence (e.g., articles in scientific journals), or any combination thereof. The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted use. *Nelson v. Bowler*, 626 F.2d 853, 857, 206 USPQ 881, 884 (CCPA 1980)."

In the present application, the previously submitted data was obtained in an art-recognized model, and thus should be sufficient to show the utility (and efficacy) of the claimed methods.

However, the combination of AVA and CpG 7909 has been tested in clinical trials, albeit not by the Applicants. Submitted herewith is a copy of the presentation by Rynkiewicz et al., "Marked enhancement of Antibody Response to Anthrax Vaccine Abosrbed with CpG 7909 in Healthy Volunteers," 2006 (available on the internet). A copy of Rynkiewicz et al. is attached for the

Examiner's convenience. This post-filing date evidence documents the unexpected efficacy achieved with ODN7909 and AVA in the macaque model system was also achieved in human subjects. The study design is shown on page 5. Healthy volunteers, age 18-45 years received treatment with Anthrax Vaccine Absorbed (AVA) alone, or AVA and CpG 7909 at days 0, 14 (2 weeks) and 28 (4 weeks). The anti-protective antigen (PA) and anti-toxin neutralizing antibody (TNA) responses of the study subjects were evaluated at several time points. The mean peak antibody concentration was 6.3-fold (anti-PA) and 8.8 fold (anti-TNA) greater in the group that received AVA and CpG 7909. In addition, the maximum anti-PA concentration was achieved in the AVA plus CpG7909 group 21 days earlier than the group that received AVA alone (see page 8). Furthermore, 12 of 22 individuals receiving AVA plus CpG 7909 were seropositive for anti-PA after a single immunization as compared to 2 of 18 subjects who received AVA alone. At peak response, 22/22 (100%) of the subjects who received AVA plus CpG 7909 had an anti-PA titer of >222 ug/ml, as compared to only 11/18 (61%) of subjects receiving AVA (see page 8). Graphical representations of this data are shown on pages 9-11. While there was a trend (the results did not achieve statistical significance) to have more severe adverse events, AVA plus CpG 7909 clearly provided a 6 to 8 fold increase and an accelerated antibody response when compared to AVA alone (see page 13).

Applicants would like to remind the Examiner that for ethical reasons, clinical trials cannot be conducted in humans on every adjuvant known to be ineffective for treatment. Thus, it is not appropriate to test other ODN that are not believed to be efficacious. However, the human data can be evaluated in comparison with the results presented in Little *et al.* (*Vaccine* 25:2771-2777, 2007, copy submitted with the prior response). Little et al. evaluated the production of anti-PA IgG antibodies in animals immunized with recombinant protective antigen (rPA) vaccine without adjuvant or with an aluminum hydroxide adjuvant. As shown in Table 2a, ten weeks after inoculation, serum antibody titers were approximately 5-fold higher in animals receiving the adjuvant, relative to vaccine alone (titers of 158 and 31.8, respectively, as measured by ELISA). Similar differences in antibody titer were observed at weeks 2, 4, 6 and 8. In contrast, administration of CpG 7909 (SEQ ID NO: 200) in combination with the AVA vaccine results in a 17-fold increase in anti-PA titer in an animal model. If the Examiner accepts the argument that the relationship of the increased effect is maintained in an animal model and a human subject, then the response in humans would be expected to be only 2-fold

greater in human (5/17 X 6-fold = 1.8 fold increase).[1] This calculation documents that the 6-8 fold increase achieved in humans was both unexpected and superior.

Thus, there were numerous unexpectedly superior effects achieved in humans using AVA and CpG 7909 (SEQ ID NO: 200), namely (1) unexpectedly superior mean peak antibody concentration; (2) an increased number of individuals achieved seropositivity with a single immunization; (3) more individual overall achieving maximum anti-PA titer; and (4) an acceleration in the antibody response. None of these unexpected superior results achieved in human subjects could be predicted based on the cited prior art.

The demonstration of results that are clearly unpredictable, unexpected and superior, both in primates and humans, overcomes any *prima facie* case of obviousness.

Reconsideration and withdrawal of the rejection are respectfully requested.

[1] If the Examiner asserts that the results in the animal model cannot be compared with humans, then the Examiner must be arguing that the clinical results could not be predicted, and therefore, are *a priori* are unexpectedly superior.

Conclusion

Applicants believe that the present claims are in condition for allowance, which action is requested. *If any issues remain prior to allowance, the Examiner is formally requested to contact the undersigned prior to issuance of an Advisory action, in order to arrange a telephonic interview prior to the issuance of any further Office action.* It is believed that a brief discussion of the merits of the present application may expedite prosecution and allowance or place the application in better condition for Appeal. This formal request for an interview is being submitted under MPEP §713.01, which indicates that an interview may be arranged in advance by a written request.

Respectfully submitted,

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